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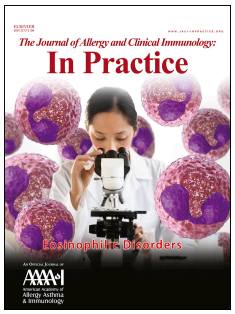

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Clinical Implications

This report provides first evidence for the IL-5Rα-blocking antibody benralizumab as a treatment option for severe DRESS not responding to first-line treatment; proteomic serum analyses point towards substantial eosinophil-and T cell-related changes induced by the treatment.

Key words:

DRESS, COVID-19, IL-5, benralizumab, eosinophils

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare severe hypersensitivity reaction that clinically manifests with exanthema, facial edema, enlarged lymph nodes, fever and organ damage at variable degrees (1). Eosinophil expansion in blood is a hallmark of DRESS and eosinophil tissue infiltration a main contributor to the observed organ damage and dysfunction (2). Although high-dose systemic glucocorticoids have not been evaluated in randomized clinical trials, they are currently the first-line therapy for DRESS with organ involvement. However, glucocorticoid-associated adverse events remain high and response rates are variable. Also, regardless of therapy, DRESS patients have a high, 5 to 10 percent, mortality rate (2). Here, we report the first use of benralizumab (Fasenra®), an interleukin (IL)-5-receptor α-chain-specific humanized monoclonal antibody (IgG1k) initially approved for eosinophilic asthma (3), in two patients with glucocorticoid-unresponsive DRESS occurring during coronavirus disease 2019 (COVID-19). The study was approved by the regional ethics review board (EK2020-01029) and conducted according to the Declaration of Helsinki.

Both patients were treated in the intensive care unit for acute respiratory distress syndrome due to COVID-19. Patient 1, a 54-year-old woman, developed prominent eosinophilia followed 3 days later by cutaneous and systemic DRESS syndrome features (Table 1). Esomeprazol and piperacillin-tazobactam (details: Figure E1a), initiated almost 6 weeks prior DRESS onset and administered intermittently, were suspected as most potential culprit drugs and stopped immediately. Patient 2, a 58-year-old man with COVID-19-related multiorgan failure developed widespread maculopapular skin lesions, facial swelling, severe eosinophilia and hepatic dysfunction. The suspected potential culprit drug in his case was midazolam, which had been administered about 3 weeks before the symptoms started (Figure E1a). In both patients, skin histopathology from cutaneous lesions on the trunk (Figure E1b) demonstrated a mostly perivascular lymphohistiocytic infiltrate and eosinophils, compatible

with a diagnosis of drug hypersensitivity reaction (1). DRESS diagnosis was based on the RegiSCAR criteria (scores 7 and 8, respectively; Table 1). In addition to discontinuing the potential culprit drugs, both patients received high-dose intravenous methylprednisolone (patient 1: 125mg for 3 days, 70mg for 4 days; patient 2: 125mg for 6 days), without improvement. In the setting of worsening eosinophilia (Figure 1a), deteriorating organ function, and exacerbation of their cutaneous eruption, the decision was made to initiate therapy with benralizumab (Fasenra®; 30mg subcutaneously). This decision was based upon the rationale that IL-5/eosinophil axis inhibition has been reported as a successful treatment in platelet derived growth factor receptor alpha-negative hypereosinophilia (4) and that IL-5, eosinophils and the eosinophil degranulation marker eosinophilic cationic protein (ECP) were highly increased. Within two days following benralizumab administration, both patients showed a rapid and substantial drop in blood eosinophils, and, as measured in patient one, ECP (Figure 1a and Figure E2). This was paralleled clinically by an improvement of the patients' cutaneous eruption, and a lowering of liver enzyme levels. Patient one continued to improve over the following 18 days. Patient two, however, developed disseminated intravascular coagulation secondary to COVID-19 and died from cardiac arrest after massive bleeding 17 days after the administration of Fasenra®.

To explore treatment-induced immunological changes, targeted serum proteomic studies were performed immediately before and one day following Fasenra® administration (Online Repository Text; Figure 1b). This analysis revealed a significant reduction in levels of IL-5, IL-4, and several proteins related to cytotoxic T cell responses and activation (CD8, tumor necrosis factor, tumor necrosis factor related apoptosis inducing ligand, signaling lymphocytic activation molecule 1 and programmed cell death 1 -ligand 1), as well as the neutrophil- and macrophage-attracting chemokines C-C Chemokine Ligand 3 and CXC Chemokine Ligand 6.

Our report suggests that IL-5Rα blockade (benralizumab) is a valuable therapeutic option in critically ill patients with massive expansion of eosinophils, if eosinophils are suspected to play a pathogenic role and symptoms exacerbate despite high-dose glucocorticoids (as a first line treatment). Additional cases and studies are needed to determine the safety and efficacy of Fasenra® and other monoclonal antibodies targeting the IL-5 axis (5, 6) in this setting.

The context, in which our DRESS cases occurred was peculiar, i.e. developing in severely affected COVID-19 patients with acute respiratory distress syndrome. It is conceivable that the severe acute respiratory syndrome coronavirus 2 contributed directly or indirectly, via induction of a cytokine storm, to the combination of eosinophilia, critical illness and eosinophil-induced organ damage (7). Eosinopenia has been shown in COVID-19 patients with a severe disease course on the other hand, but it remains to be elucidated whether this association is pathophysiologically relevant or rather incidental (8).

IL-5 is mainly produced by T helper 2 cells and is a critical mediator responsible for differentiation, activation, and, in synergy with other mediators, chemotaxis of eosinophils (9), which considerably contribute to organ damage in DRESS. Our hematologic and proteomics data suggest that Fasenra® had a rapid and profound effect on eosinophils. It also points towards a benralizumab-mediated indirect regulatory effect on other cell types, possibly cytotoxic T cells. It remains to be elucidated whether a similar dynamic is observed in other conditions during IL-5Rα blockade.

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142 **Figure legends**

143

144 **Figure 1. Serological changes during benralizumab therapy.**

145 a) Line graphs showing counts ($x10^9$ / L) of the indicated leukocytes (measured daily) over
146 the course of DRESS diagnosis and treatment in patient one and patient two, respectively. b)
147 Heatmap showing significantly up- and down-regulated proteins (identified by Olink
148 proteomics; $p<0.05$) in patient one and two prior (day 0) and after (day 1) treatment with
149 benralizumab.

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151

152 **Table 1. Patient details.**

	Patient 1	Patient 2
General information		
Sex	female	male
Age (years)	54	58
Ethnicity	Caucasian (Central Europe)	Asian (China)
Pre-existing conditions	Diabetes mellitus type 2	Diabetes mellitus type 2 Multinodular goiter Moderate allergic asthma
COVID-19-related information		
COVID-19 diagnosis prior DRESS onset (days)	42	29
Intubation (due to ARDS) prior DRESS onset (days)	32	23
Sars-CoV2 RT-PCR at the time of DRESS diagnosis	negative	negative
Medications for COVID-19	Lopinavir/Ritonavir Hydroxychloroquine	Hydroxychloroquine
Complications from COVID-19	ARDS Pulmonary embolism Heparin-induced thrombocytopenia Multiple venous thrombosis Megacolon with focal ischemia Hepatopathy	ARDS Hemorrhagic shock from upper gastronintestinal bleeding Acute renal insufficiency (AKI 3) Catheter-associated thrombosis Hepatopathy

DRESS characteristics

RegiSCAR DRESS Score	7	8
Detailed DRESS features (at the time of diagnosis)		
Skin eruption >50% Body surface area	Maculopapular exanthema	Maculopapular exanthema
Fever	Yes	Yes
Lymphadenopathy	No	Yes
Eosinophilia	> 1.5 x 10^9 / L	> 1.5 x 10^9 / L
Atypical lymphocytes	None	None
Organ involvement; lab values at the time of diagnosis		
Kidney	No; serum creatinin 40 µmol/l: eGFR 114 ml/min	Yes; serum creatinin 142 µmol/l: eGFR 47 ml/min
Liver	Yes; AST 196 U/l; ALT 263 U/l	Yes; AST 106 U/l; ALT 125 U/l
Lung	Yes; ARDS	Yes; ARDS
Heart / Muscle	Yes; myoglobin 129 µg/l	Yes; myoglobin 813 µg/l
Pancreas	No; pancreatic amylase 7 U/l	No; pancreatic amylase 6 U/l, lipase 7 U/l
Other	None	None
Viral serologies at DRESS diagnosis (HHV6, EBV, CMV, HSV1/2, VZV)	Negative	Negative
Skin histopathology suggestive for DRESS	Yes	Yes
Previous history of drug	None	None

allergies		
First-line DRESS treatment	Intravenous methylprednisolone (125mg 4 days, 70mg 3 days)	Intravenous methylprednisolone (125mg 3 days)
Outcome	Alive; still hospitalized (day 28 after DRESS diagnosis)	Death from cardiac arrest after hemorrhagic shock (day 17 after DRESS diagnosis)

153 ARDS: Acute respiratory distress syndrome; RT-PCR: real-time PCR; Sars-CoV2: severe
154 acute respiratory syndrome coronavirus 2. Normal ranges of laboratory test values: serum
155 creatinine: 62-106 μmol/l; creatinin kinase: <190 U/L; myoglobin: 28-72 μg/l; AST and ALT:
156 <50 U/l; pancreatic amylase: 13-52 U/l; lipase: 13-60 U/l

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Figure 1

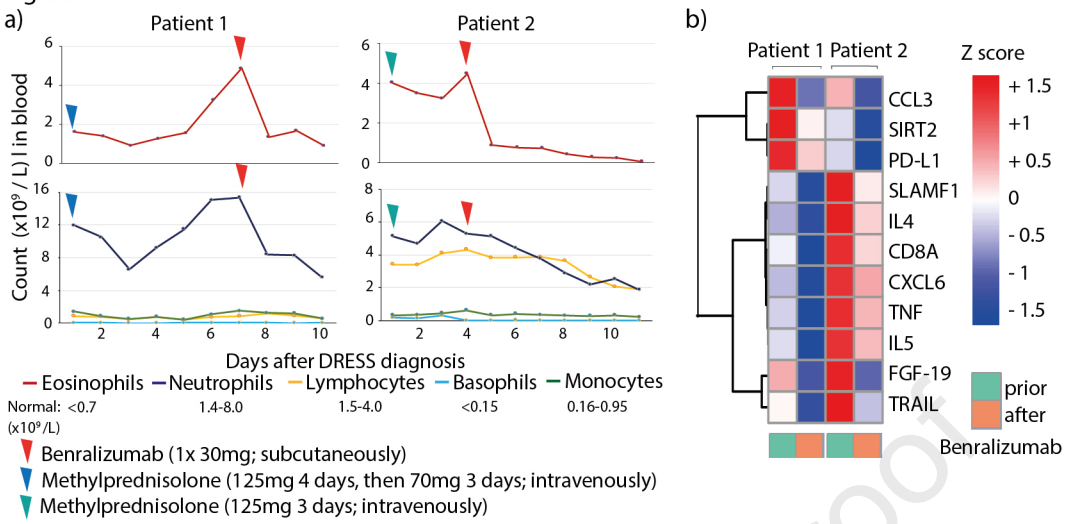


Figure E1

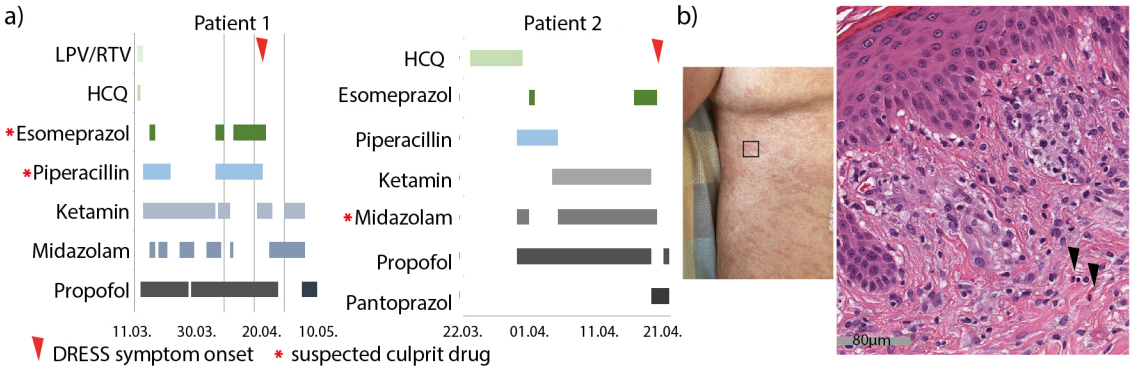
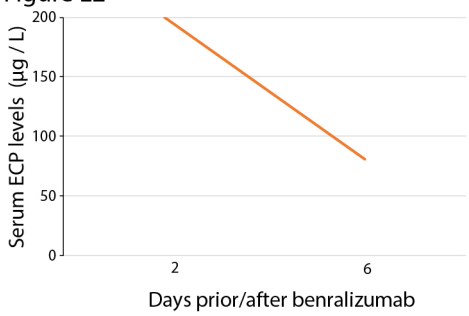


Figure E2



Online Repository: Material and Methods

Ethics Approval

The study was approved by the regional ethics review board (EK2020-01029) and conducted according to the Declaration of Helsinki.

Sample preparation

Blood was collected using serum tubes. Samples were processed immediately after collection and stored at -80 Celsius until further processing.

Protein quantification in blood

The proteomic Proseek multiplex assay by Olink (Uppsala, Sweden) is a proximity extension assay with oligonucleotide-labeled antibody probe pairs. It measures proteins via an antibody-mediated detection system linked to synthetic DNA for quantification by a real-time polymerase chain reaction platform.

Statistical analysis of Olink data

Olink data in Normalized protein expression (NPX) format were imported, processed by OlinkRPackage from Olink Proteomics (https://github.com/Olink-Proteomics/OlinkRPackage). The statistical comparison of protein levels between groups was performed with Bioconductor limma package (https://bioconductor.org/packages/release/bioc/html/limma.html). The fold change and p-value were estimated by fitting a linear model for each protein.

Figure Legend of Figure E1.

a) Timelines for the respective medications of patient one and patient two. Abbreviations used: LTV: lopinavir; RTV: ritonavir; HCQ: hydroqychloroquine. b) Hematoxylin/eosin staining from lesional skin of patient two (on the trunk, framed area on the photograph). Histopathology showing vacuolar changes of the basal layer and a mostly perivascular, lymphohystiocytic infiltrate with few admixed eosinophils (indicated by arrows) in the upper dermis.

Figure Legend of Figure E2.

Levels of eosinophilic cationic protein (ECP) prior (day 0) and at day two after benralizumab treatment in patient 1. The dashes line corresponds to the upper normal limit (l13.3 µg/L). On day 0, ECP levels exceeded the maximal measuring range (200 µg/L).